Remarks/Arguments

Claims 140-144, 146-150, 153 and 156-173 are pending in the application. Reconsideration is respectfully requested.

Claim Rejections-35 U.S.C. §112

The Examiner has rejected claims 140-144, 146-150, 152, and 156-171 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states that claim 140 is indefinite because it claims an amount of particulate epinephrine of "at least about 50 micrograms" possessing a fine particle fraction of less than 5.6 microns of "at least about 45 percent. The Examiner asserts that the phrase "at least about" is indefinite because it simultaneously claims two different ranges. The Examiner states that the skilled person would be unable to assess whether the required amount of epinephrine is at "least about 50 micrograms" or "about 50 micrograms". Applicants respectfully disagree.

The skilled practitioner would clearly understand that two ranges are not being claimed. Given that the claimed invention is directed to a method for highly efficient delivery there is nothing confusing about setting a relative lower limit of "at least" 50 micrograms and "at least" 45% FPF. The fact that the term "about" is inserted before "50 and "45%" merely indicates to the skilled practitioner that the lower limit can not be articulated given for example, that data points do not always appear in whole numbers.

According to MPEP §2173.05(b)(A), the term "at least about" in a claim was determined to be indefinite when there was close prior art and there was nothing in the specification, prosecution history or the prior art to provide any indication as to what range of specific activity is covered by the term "about". However the facts in the present application are very different. There is no close prior art that discloses highly efficient delivery of epinephrine in any rang (see discussion below). In addition, the specification itself discloses on page 56 lines 4-10 that preferred ranges of epinephrine particles delivered to the patient include at least about 50, but preferably even more. The specification also discloses on page 36, lines 5-10 that FPF 5.6 has been demonstrated to correlate to the fraction of powder that reaches the lung of the patient. The examples in the application provide data showing that FPF is often much higher than 45% as is the dose of epinephrine in micrograms as described in the human clinical studies of the

examples. Thus the specification provides the skilled practitioner with more than enough information to readily understand what specific activity is included in the term "at least about" as it is used in the claims. The scope of the claims is clear, and the rejection is improper. Withdrawal of the rejection is respectfully requested.

Claim Rejections-35 U.S.C. §103

Claims 140-144, 153, and 156-160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tarara et al., (US 2005/0074498) in view of Slutsky et al. (U.S. Patent No. 6,102,036). The Examiner relies on his description of the teachings of Tarara as set forth on pages 3-5 of the office action dated April 6, 2006. The Examiner has since added Slutsky to the rejection. The Examiner states that Slutsky teaches a breadth activated inhaler which is intended to be inhaled by the patient in a single breath and which is capable of delivering a large dose of powdered medicament in a single breadth. The Examiner concludes that it would have been obvious to combine the teachings of Tarara and Slutsky because Tarara teaches powdered formulations for inhalation and Slutsky teaches breath activated inhalers and Slutsky's inhaler would allow one to deliver a large dose in a single breath. The Examiner further asserts that the combination of Tarara's compositions with Slutsky's invented inhaler would reasonably be expected to deliver at least 50 micrograms of epinephrine, because one can modify the dosage of epinephrine present in the inhaler to ensure the delivery of a therapeutically amount of epinephrine and Slutsky's inhaler permits delivery of an entire dose in a single breath. Applicants respectfully disagree.

The Examiner's reliance on Slutsky to teach a "new" breath activated inhaler capable of delivering a "large" dose in a single breath does no more to make the present claims obvious than did Tarara alone. For all the reasons discussed on pages 4-8 of the Appeal Brief filed by Applicants on April 25, 2007, Tarara does not make obvious the presently claimed invention. As discussed on page 8 of Applicants Appeal Brief dated April 25, 2007, with respect to the limitation that the administration be achieved in a single breath, the Examiner has not provided any motivation as to why one skilled in the art would combine epinephrine (mentioned in a long list in Tarara), with delivery via a breath activated inhaler in a single breath-activated step and yet deliver with the claimed

high efficiency, despite the patient's likely severe respiratory distress. Slutsky merely discloses a (modified) breath activated inhaler. The fact that single-breath activated inhalation devices such as Slutsky's were in the prior art was disclosed by Applicants on page 57, lines 14-21 of the present specification. Slutsky also makes reference to those same prior art inhalers at column 6, lines 16-27, and discloses that the inhaler invented by therein is in fact a modified form of these standard inhalers (see column 6, lines 28-60, and column 7 lines 20-34 describing the modification to the known inhalers of the prior art). Thus the disclosure by Slutsky of yet another breath activated inhalation device, does no more to make obvious the presently claimed invention than Tarara did alone. It is noted that DPIs of any type were viewed in the art to have many drawbacks related to their reliance on inspired air from the patient. See for example column 1, lines 51-57 of U.S. Patent No. 5, 458,135 (submitted as Exhibit A in Applicant's Appeal Brief dated April 25, 2007) where the many disadvantages of DPIs are described. Without the benefit of hindsight in view of the present invention, one skilled in the art would not be motivated to rely on a breath-actuated dry powder inhaler to deliver a life saving drug in a crisis situation that also involved difficulty in breathing.

In addition, Slutsky's modifications to the inhaler render the single breath-activated inhaler *less suitable* for the delivery of epinephrine to a patient in crisis having difficulty breathing. Slutsky's modifications the breath activated inhalers of the prior art are intended to *restrict* the cross-sectional area of the air conduit so as to *reduce* the flow rate of air (column 7 lines 14-34). The assumption by Slutsky is that the prior art inhalers have low resistance because they are being used by a person having difficulty breathing, but for patients requiring nicotine who are not in respiratory distress, the absence of resistance by a healthy breath could cause impaction of nicotine at the back of the throat (Column 7, lines 14-23). Thus Slutsky modifies the inhaler to restrict the air flow and increase resistance. Clearly, one skilled in the art would not be motivated to combine Slutsky's inhaler which is intended to restrict the flow rate of nicotine to a healthy breather with a therapeutic such as epinephrine intended for delivery in a crisis situation to a person who is having difficulty breathing.

For the reasons discussed above, the combination of Tarara with Slutsky does not make obvious the presently claimed invention. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has rejected claims 161-162 under 35 U.S.C. §103(a) as being unpatentable over Tarara et al. in view of Slutsky (U.S. Patent No. 6,102,036) as applied to claims 140-144, 153, and 156-160 above and further in view of the 56th edition (2002) of the Physician's Desk Reference (hereinafter the "PDR") already of record. Applicants respectfully disagree.

Claims 162 and 163 depend from Claim 140 and further define the patient to be treated (i.e., a patient suffering from anaphylaxis (Claim 161) and a patient suffering bronchoconstriction, bronchospasm, airway constriction, or edema (Claim 162)). Tarara and Slutsky are relied upon as above and for the reasons discussed above, do not make obvious claim 140. The PDR is relied upon to show that epinephrine is known to treat these diseases.

While it is not disputed that the PDR establishes that epinephrine is known to treat these diseases, it is not conceded that it would be obvious to treat these kinds of diseases by pulmonary delivery of the product that is described above in Claim 140. Given the high efficencies in delivery and the large cloud that will result from the actuation of a highly efficient and large dose, it is not at all obvious to treat a patient suffering from anaphylaxis (Claim 161) and a patient suffering bronchoconstriction, bronchospasm, airway constriction, or edema (Claim 162). The fact that the PDR suggests that the drug is known to be administered for a given disease does not necessarily support a conclusion that any and all modes of administration of that drug would be obvious.

Therefore, the cited combination of references does not make claims 161-162 obvious. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has rejected claims 140-143, 146-150, 159-160 and 162 under 35 U.S.C. §103(a) over Foster (U.S. 2003/0215512) in view of Tarara and Slutsky. The Examiner relies on the teachings of Tarara as set forth on pages 8-10 of the office action mailed on April 6, 2006. The Examiner states that Foster lacks the teaching of compositions having a tap density of less than 0.4 g/cm^3 which is cured by the teachings

of Tarara. The Examiner also states that Foster lacks the teaching of administration in a single breath activated step which is cured by Slutsky. The Examiner further asserts that one would have motivated to combine Foster and Tarara because Tarara's compositions provide aerodynamically light particles suitable for inhalation. The Examiner also asserts that the skilled person who is aware of Slutsky would be motivated to use Slutsky's breath activated inhaler to improve patient compliance and delivery active agent in the fewest number of administration. The Examiner concludes that one would expect success upon combination as both Tara and Foster teach epinephrine for pulmonary administration. Applicants respectfully disagree.

Throughout this entire prosecution, the Examiner has refused to view the present claims as a whole and has continued to ignore claim limitations. The Examiner has not provided any motivation as to why one skilled in the art would combine epinephrine (mentioned in a long lists in both Foster and Tarara), with a single, breath-activated inhalation and expect to deliver with high efficiency, 50 micrograms of epinephrine to a patient who is in need of epinephrine, and, thereby is likely to be in severe respiratory distress. While Slutsky mentions that the dose of *nicotine* (not epinephrine) can be as high as 10 mg, neither Slutsky nor Tarara/Foster teach highly efficient administration of any therapeutic product (products having an FPF of less than 5.6 microns of at least 45% in a single breath) to any patient including normal healthy patients. In fact Slutsky provides no data whatsoever in which the efficiency of delivery can be determined and provides no discussion of FPF or other information that correlates to delivery efficiency. Slutsky merely asserts that large doses can be delivered in a single breath. And contrary to the Examiner's assertions, one skilled in the art would not be motivated to use Slutsky's breath-activated inhaler to delivery epinephrine in any case, because Slutsky's inhaler is designed to restrict airflow for use by patients who do not have obstructed airways. Clearly the skilled practitioner would not choose an inhaler that would restrict a patient's inhalation of epinephrine, given that the patient in need of epinephrine is having difficulty breathing at the time the epinephrine is required.

Therefore, in view of the above discussion, the cited combination of Tarara, Foster and Slutsky does not make the present invention obvious. Withdrawal of the rejection under this section is respectfully requested.

The Examiner has rejected claim 171 under 35 U.S.C. §103(a) as being unpatentable over Tarara, in view of Slutsky as applied to claims 140-144,153 and 156-160 above, and further in view of Radhakrishnan (U.S. Patent No. 5,049,389) already of record. The Examiner relies on Tarara and Slutsky as above. The Examiner states that the teachings of Radhakrishnan were set forth on page 10 of the office action mailed on April 6, 2007. The Examiner states that Tarara lacks the teaching of compositions releasing active agents in a sustained manner which is cured by the teachings of Radhakrishnan. The Examiner asserts that it would have been obvious to combine Radhakrishnan and Tarara to obtain sustained release compositions wherein the active drug and excipients do not crystallize within the liposome and which do not undergo sedimentation when suspended. The Examiner concludes that one would expect success because both inventors teach particular compositions for inhalation comprising adrenaline. Applicants respectfully disagree.

Contrary to the Examiner's assertion, neither Radhakrishnan nor Tarara *teach* "particular" compositions for inhalation comprising adrenaline. Without the benefit of hindsight, one would not have been motivated to choose adrenaline from amongst the many active agents listed in both Radhakrishnan and Tarara. Furthermore, the problem that Radhakrishnan wishes to solve (sedimentation on resuspension) is a problem encountered upon using a liquid-based nebulizer, not a dry powder inhaler. As such, one of ordinary skill in the art would not combine Radhakrishnan with Tarara and Slutsky to arrive at the claimed method which relies upon the use of a dry powder inhaler. In addition, claim 171 is dependent from claim 140 and includes all the features of claim 140. For all the reasons discussed above, claim 140 is not obvious in view of any of the above cited combination of references; therefore the Examiner's reliance on the teachings of the secondary references is rendered moot. In view of the above, withdrawal of the rejection under this section is respectfully requested.

The Examiner has finally rejected Claims 163-170 under 35 U.S.C. §103(a) over Tarara in view of Slutsky as applied to claims 140-144, 153 and 156-160 above, and further in view of Warren et al. (*Clin. Pharmacol. Ther.* (1986) **40**(6), 673-678) already of record. It is stated that Tarara lacks the express teaching of Cmax and Tmax of

different administration routes. The Examiner relies upon Warren to show that inhalation of 30 puffs (i.e., not in a single breath) of adrenaline from a pressurized aerosol (not a breath actuated dry powder inhaler) are indicative of what one would expect upon inhalation of Tarara's formulations. The Examiner asserts that based on Warren's data, one would have been motivated to administer epinephrine to a patient and would have had a reasonable expectation that the such administration would result in maximal adrenaline blood serum levels in a shorter period of time when compared administration by injection. Applicants respectfully disagree.

Warren does not suggest or disclose that it would be obvious to administer epinephrine by a breath actuated dry powder inhaler. The inhaler of Warren relies upon the external energy of a propellant to disperse the drug and then a large number of breaths to deliver the drug. In addition, claims 163-170 are dependent from claim 140 and include all the features of claim 140. For all the reasons discussed above, claim 140 is not obvious in view of any of the above cited combination of references. Warren, as the secondary reference, provides no substantive teachings that a highly efficient dose of epinephrine can be achieved in a single breath actuated administration from a dry powder inhaler. In view of the above, withdrawal of the rejection under this section is respectfully requested.

The Examiner has rejected Claims 172 and 173 under 35 U.S.C. §103(a) as being unpatentable over Foster in view of Tarara and Slutsky and further in view of Drug Information Handbook ("DIH"). The Examiner relies on the teachings of Foster, Tarara and Slutsky as above and relies on the teachings of the DIH as set forth in the office action mailed on April 6, 2006. The Examiner states that the use of epinephrine bitartrate would have been apparent to a skilled artisan because it is "one of the most common salts of epinephrine employed in pharmaceutical formulations." The Examiner relies upon Foster to teach adding a glass former, such as tartrate, and an additional excipient such as leucine in the formulation. Regarding the amounts of each ingredient, the Examiner asserts that the teaching in Foster of a range of 0.05% to 99.0% active agent makes obvious the selection of 11 to 21% epinephrine bitartrate and, with respect to the remaining excipients, it is a parameter that is routinely optimized.

While both Foster and Tarara mention adrenaline (epinephrine) as part of a long list of actives, the mere fact that both references disclose overlapping lists of active agents for incorporation of particles does not provide the skilled practitioner with an expectation of successfully mixing and matching specific excipients and active agents in specific amounts. Neither reference discloses or suggests the desirability of producing the specific epinephrine formulation of claims172 and 173 nor has the Examiner provided any evidence that would motivate the skilled practitioner to combine the teachings of Foster and Tarara and Slutsky in order to prepare epinephrine containing particles. The Examiner has merely concluded that because both references mention both "particles" and "adrenaline" that they should be combined. This is improper.

The specific formulations are not reasonably taught by Foster or the primary reference, alone or when combined with Tarara and Slutsky and the DIH. Foster teaches a nearly infinite number of possible combinations of a large number of active agents and a large number of excipients. There is no guidance within Foster's broad generic disclosure to couple epinephrine bitartrate, leucine and sodium tartrate in the specific amounts claimed.

The preferred active agents of Foster appear to be proteins, polypeptides and other macromolecules. Although small molecule drugs are also described and may be "adrenalin," specific salts thereof are not disclosed. It is noted that salts of many drugs are described in the same list. Had Foster intended to teach salts of epinephrine, he would have. With respect to the amount of active agent added, the reference's range of 0.05% to 99.0% by weight of active agent is, essentially meaningless because it spans the entire range of possible amounts. That is, it is difficult to imagine a therapeutically effective product where the amount of active agent is substantially lower than 0.05%. Further, since Foster appears to rely upon the formation of a glassy matrix and since the Examiner has not shown that epinephrine would be expected to be glassy, it is not clear that Foster teaches a 99.0 or 100% epinephrine formulation. In any event, a range of essentially no active agent to essentially all active agents is not a meaningful teaching of any particular amount of drug to add. The preferred range of between 0.2% and 97% is hardly more meaningful. Para. [0054]. Such a range hardly suggests to the person of skill

in the art to select the range between 11 and 21%. The only small molecule working examples carried less than 5% drug. See Example 16.

The excipients of Foster span several columns. The Examiner relies upon the teaching of adding a "glass former" to suggest that sodium tartrate can be added. In fact, the reference suggests that any glass former can be used and, where the drug itself forms a glass, can be omitted altogether. Para. [0064]. Sodium tartrate is one of several glass formers that could be used, in addition to peptides, carbohydrates such as mannitol (when used in combination with, for example, glycine) or lactose, citric acid and sodium citrate. Sodium citrate was the structurally closest glass former actually used. However, it appears that all of the working examples employed large amounts of glass formers, in various combinations. There is no guidance to select between about 7 and 17% of this particular compound. There is no suggestion that this particular combination would be expected to result in a glassy matrix.

Furthermore, the claims require the addition of a large amount of leucine. Leucine is not disclosed as a preferred excipient (or "additive") and there is no guidance in this reference which would suggest that it would be desirable to select leucine and add it in a large quantity. The amount of any one excipient is also not described in a meaningful way to suggest a preferred amount as the teachings are limited to 3% to 99.8% by weight [Para. [0079]]. In fact, this passage suggests that such "additives" should be added in an amount less than 20% w/w. The claims require the leucine to be added in an amount between about 62 and 82%. The reference simply provides no motivation to add such a substantial amount of leucine.

Turning to the working examples for meaningful guidance, 66.2% mannitol, 13.1% sodium citrate and 0.7% citric acid was used with 20% zinc-insulin in Example 1; 18.2% mannitol, 59.1% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 2; 10.1% mannitol, 27.1% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 3; 18.3% mannitol, 19.0% sodium citrate, 0.2% sodium ion and 2.6% glycine was used with 60% zinc-insulin in Example 4; 77.3% sodium citrate, 0.1% citric acid and 2.6% glycine was used with 20% zinc-insulin in Example 5; and so on. Not one example employs an amino acid at high concentrations; not one example employs either leucine or sodium tartrate; not one

example employs epinephrine, much less epinephrine bitartrate. A sugar is present in almost every working example. The vast majority of the working examples formulate a protein or peptide. Albuterol sulfate, the only small molecule exemplified, was formulated with 95% or 98% lactose. There is simply no motivation in this exceedingly broad disclosure of a nearly infinite number of possible combinations to select the specific excipients of the claims, in the specific amounts and combine them with epinephrine.

With regard to the addition of Slutsky as a secondary reference, as discussed above, Slutsky provides no more information about the prior art inhalers than is already disclosed in the present specification. Moreover, the modifications to the prior art breath activated inhalers disclosed in Slutsky are intended for patients with unobstructed breathing. Clearly the skilled practitioner would not choose an inhaler as provided by Slutsky that would restrict a patient's inhalation of an epinephrine, given that the patient in need of epinephrine is having difficulty breathing at the time the epinephrine is required.

More is required to support a *prima facie* case of obviousness than the mere fact that the words of the claim can be found within reference and the unsupported assertion that the rest that is missing from the reference is mere routine optimization. See *In re Baird*, 16 F.3d 380, 382; 29 USPQ2d 1550 (CCPA 1979).

Conclusion

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 251-3509.

Respectfully submitted,

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